The present rejection is based on misinterpretations of Kingsmore et al. and of the claimed method. Kingsmore et al. does not disclose what is alleged in the Office Action and does not disclose what is presently claimed. As a result, Kingsmore et al. fails to disclose every feature of the present claims. This error renders the rejection legally flawed with the result that the Office Action fails to establish a prima facie case of anticipation. In making a rejection under 35 U.S.C. § 102, the Patent Office is burdened with establishing that the cited art teaches each and every limitation of the claims. The present rejection does not meet this burden.

Kingsmore et al. discloses a method for detecting analytes involving bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule binds to the analyte. An amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. Kingsmore et al. fails to disclose decoupling of the amplification target circle from the reporter binding primers. In fact, in the method of Kingsmore et al. the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with the reporter binding primer during replication.

Applicants claim a method of detecting analytes that involves, *inter alia*, association of reporter binding molecules (which each comprise a specific binding molecule and an amplification target circle) with analytes. The amplification target circles are replicated to produce tandem sequence DNA. Significantly, however, the amplification target circles are **decoupled** from the reporter binding molecules prior to replication (see step (b) of claim 1; step

(c) of claims 107, 108, and 110; lines 8-9 of claims 124 and 133; lines 12-13 of claim 134; lines 10-11 of claim 135; and lines 13-14 of claim 136). As described in the present application:

> decoupling refers to physical disunion of one molecule or component from another (as for example, decoupling of an amplification target circle from a reporter binding molecule). It is specifically contemplated that decoupling refers to the physical disunion both of molecules or components that are covalent couple [sic] to each other and molecules or components that are non-covalently associated with each other. In the former case, decoupling will generally involve cleavage of one of more covalent bonds. In the latter case, decoupling will generally involve dissociation.

Page 16, lines 19-26 of the application.

Applicants submit that Kingsmore et al. does not disclose any step of decoupling of an amplification target circle as required by the claims. No step in Kingsmore et al. corresponds to decoupling of an amplification target circle within the meaning of the term "decoupling" in the present application (see page 16, lines 19-26). At least because Kingsmore et al. fails to disclose decoupling of the amplification target circle from the reporter binding primers, Kingsmore et al. fails to disclose every feature of the claimed method. Accordingly, Kingsmore et al. fails to anticipate claims 1, 12-113 and 118-136.

Response to Specific Bases of the Rejection

1. The Office Action argues (page 3, lines 8-16) that Kingsmore et al. discloses decoupling of the amplification target circle from reporter binding molecules in Example 7 (column 36, lines 21-27), noting that the cited passage discloses "decoupling the circles from reporter binding molecules using capture agents (anti-antibody IgE)" prior to replication of the circles. Applicants submit that this is incorrect. Example 7 does not involve any decoupling of circles from reporter binding agents, does not involve decoupling of circles from reporter binding

agents prior to replication of the circles, and does not involve decoupling of any component "using capture agents."

Applicants submit with this Response a diagram (Appendix A) illustrating the method described in Example 7 of Kingsmore et al. Lines 21-27 of column 36 in Kingsmore et al. describe the subject matter of steps 2 and 3 in Appendix A. As can be seen, the circles become associated with primers (Pr1 and Pr2) on the antibody-primer conjugates Pr2-Mab Anti-IgE and Pr1-Mab Anti-biotin in step 3. The circles do not become dissociated (or decoupled) from the Mab conjugates at either of steps 2 or 3, nor do the circles become dissociated from the Mab conjugates at any other step in the method of Example 7. Further, the circles are not associated with any component in the method of Example 7 prior to step 3 and thus are not dissociated (or decoupled) from any component prior to step 3. The inescapable conclusion is that there is no dissociation or decoupling of the circles in Example 7 at any point. For at least this reason, Kingsmore et al. fails to disclose every element of the claimed method.

The reference to "decoupling the circles from reporter binding molecules using capture agents (anti-antibody IgE)" in the Office Action does not make sense. As can be seen in Appendix A, the "anti-antibody IgE" in Example 7 of Kingsmore et al. are used (1) to form complexes of IgE (antigen) and antibodies (anti-IgE antibodies) (see step 1) prior to (2) capture (immobilization) of these antigen-antibody complexes on the microarray (see step 2). There are no circles present in these steps, no separation or other removal, dissociation or decoupling of any circles in these steps, and no decoupling of any component from any other in these steps. Thus, the key evidence presented in the Office Action to support the present rejection bears no relationship to the claim feature purportedly taught. This clear error renders the rejection

insufficient and unsupportable. Because the rejection fails to make a prima facie case of anticipation by failing to identify any teaching or disclosure in Kingsmore et al. of the claimed decoupling step the present rejection is unsupportable and should be withdrawn.

2. The Office Action also asserts (page 3, lines 16-21; page 4, lines 14-17) that Kingsmore et al. discloses separation of components (using, for example, capture agents) and that "this clearly suggests separation is an alternative for decoupling." The Office Action is thus equating separation and washing steps with the claimed decoupling step. Applicants submit that this is both incorrect and legally impermissible. Although Kingsmore et al. does disclose separation of some components and washing of bound reaction components, neither of these steps is the same as the claimed decoupling step.

In the claimed method, a reporter binding molecule (which is a multi-component complex made up of both a specific binding molecule and an amplification target circle) is associated with an analyte and then a part of the reporter binding molecule (the amplification target circle) is decoupled from the reporter binding molecule. That is, the former association of the specific binding molecule and amplification target circle is broken (see page 16, lines 19-26 of the specification where decoupling is referred to as a physical disunion of the amplification target circle from the reporter binding molecule). The cited passages of Kingsmore et al. do not disclose such broken associations or physical disunions. Rather, the separation and washings of Kingsmore et al. merely separate already unbound and unconjugated components from each other.

There is no suggestion in the cited passages of Kingsmore et al. that indicates or suggests that the separation (using, for example, capture agents) or washings involve any dissociation or

decoupling of any component from any other. Rather, the separation and washing steps of Kingsmore et al. refer to separation or washing of components or conjugates that are not bound, conjugated or coupled to the components from which they are being separated. This is different from the claimed decoupling step. The rejection fails to resolve this key discrepancy between the claimed decoupling step and the separations and washings referred to in Kingsmore et al. Because the relevance of the separations of Kingsmore et al. to the claimed decoupling step is not provided in the rejection and because the separations of Kingsmore et al. are not in fact relevant to the claimed decoupling step, the separations of Kingsmore et al. do not support a prima facie case of anticipation. Simply put, a prima facie case of anticipation cannot be established by an unsupported assertion that a step in the cited art is the same as a claimed step, especially when the two steps are clearly different and unrelated.

The Office Action also makes several references to "capture agents" and to their use in separations (implying that capture agents could be involved in or used for "decoupling" amplification target circles). As described in Kingsmore et al., capture agents are used to immobilize or "capture" analytes (see, for example, col. 14, lines 25-50 of Kingsmore et al.). This has nothing to do with dissociation or decoupling of an amplification target circle from a reporter binding molecule. Because the relevance of capture agents to the claimed decoupling step is not provided in the rejection and because the capture agents of Kingsmore et al. are not in fact relevant to the claimed decoupling step, the capture agents of Kingsmore et al. do not support a prima facie case of anticipation.

3. The claimed method involves, *inter alia*, (1) association of reporter binding molecules (which each comprise a specific binding molecule and an amplification target circle) with

analytes, (2) separation of the specific binding molecules (which are part of the reporter binding molecules) that interact with analytes from those that do not, (3) decoupling the amplification target circles from the reporter binding molecules that interact with the analytes, (4) bringing the amplification target circles and rolling circle replication primers into contact, and (5) rolling circle replication of the amplification target circles. In listing alleged teachings of Kingsmore et al. that allegedly account for all of the elements of the claimed method (paragraph bridging pages 4 and 5 of the Office action), the Office Action states that "Kingsmore et al. teach a method...comprising...(b) decoupling or separating analytes using capture agents or separating analytes using capture agents after interaction of analyte samples with reporter binding molecules, thus separating analytes...." This equates, without basis, decoupling and separation (see discussion above on this point) and further seems to assume that the that the separation step and the decoupling step of the claimed method are somehow equivalent, interchangeable or otherwise the same step. This is not the case.

The claimed method requires, as separate and distinct steps, both (1) separation of the specific binding molecules that interact with the analytes from the specific binding molecules that do not interact with the analytes (see, for example, lines 8-9 of claim 1) and (2) decoupling the amplification target circles from the reporter binding molecules that interact with the analytes (see, for example, step (b) of claim 1). The Office Action has not only failed to point to any disclosure of a decoupling step in Kingsmore et al., the Office Action also fails to recognize that the claimed method requires both a separation step and a separate, distinct decoupling step. Even if the decoupling step constituted a "separation" (it does not as discussed above), Kingsmore et al. does not disclose the use of a separation step followed immediately by a

second, separate "separation" (decoupling) step. Thus, for at least these reasons, Kingsmore et al. fails to disclose a method having even the number and order of the claimed steps. For at least this additional reason, Kingsmore et al. fails to anticipate claims 1, 12-113 and 118-136.

For all of the above reasons, Kingsmore et al. fails to anticipate claims 1, 12-113 and 118-136.

Rejection Under 35 U.S.C. § 103

Claims 2-11 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kingsmore et al. (U.S. Pat. No. 6,531,283), in view of Lizardi et al. (U.S. Pat. No. 6,403,319). Applicants respectfully traverse this rejection.

The present rejection is based on misinterpretations of Kingsmore et al. and of the claimed method. Kingsmore et al. does not disclose or suggest what is alleged in the Office Action and Kingsmore et al. and Lizardi et al., either alone of in combination, do not disclose or suggest what is presently claimed. As a result, Kingsmore et al. and Lizardi et al., either alone of in combination, fail to disclose every feature of the present claims. This error renders the rejection legally flawed with the result that the Office Action fails to establish a prima facie case of obviousness. In making a rejection under 35 U.S.C. § 103, the Patent Office is burdened with establishing that the cited art teaches or suggests each and every limitation of the claims. The present rejection does not meet this burden.

Kingsmore et al. discloses a method for detecting analytes involving bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule binds to the analyte. An amplification target circle is brought into contact with the rolling circle replication primer

(which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. Kingsmore et al. fails to disclose or suggest decoupling of the amplification target circle from the reporter binding primers. In fact, in the method of Kingsmore et al. the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with the reporter binding primer during replication.

Lizardi et al. discloses a method of analyzing nucleic acid sequences by amplifying nucleic acids with primers able to form a hairpin structure. The hairpin structure (which forms in the amplified nucleic acid strands) allows the amplified nucleic acid strands to be covalently coupled to probes in an array. The probes in the array can interact with the amplified nucleic acid strands via base pairing. Lizardi et al. fails to disclose or suggest an amplification target circle that is part of a reporter molecule of any sort. Lizardi et al. also fails to disclose or suggest decoupling of an amplification target circle from any molecule or component.

Applicants claim a method of detecting analytes that involves, *inter alia*, association of reporter binding molecules (which each comprise a specific binding molecule and an amplification target circle) with analytes. The amplification target circle of at least one of the reporter binding molecules is associated with the reporter binding molecule via a non-covalent interaction with circle capture probe that is a part of the reporter binding molecule (see claim 2). The amplification target circles are replicated to produce tandem sequence DNA. Significantly, however, the amplification target circles are **decoupled** from the reporter binding molecules prior to replication (see step (b) of claim 1). As described in the present application:

> decoupling refers to physical disunion of one molecule or component from another (as for example, decoupling of an amplification target circle from a reporter binding molecule). It is specifically contemplated that decoupling refers to the physical disunion both of molecules or components that are covalent couple [sic] to each other and molecules or components that are non-covalently associated with each other. In the former case, decoupling will generally involve cleavage of one of more covalent bonds. In the latter case, decoupling will generally involve dissociation.

Page 16, lines 19-26 of the application.

Applicants submit that Kingsmore et al. does not disclose any step of decoupling of an amplification target circle as required by the claims. No step in Kingsmore et al. corresponds to decoupling of an amplification target circle within the meaning of the term "decoupling" in the present application (see page 16, lines 19-26). At least because Kingsmore et al. fails to disclose decoupling of the amplification target circle from the reporter binding primers, Kingsmore et al. fails to disclose every feature of the claimed method. The Office Action does not allege that Lizardi et al. discloses or suggests the claimed decoupling step. Accordingly, Kingsmore et al. and Lizardi et al., either alone of in combination, fail to make obvious claims 2-11.

The Office Action refers to the reasons presented in rejection under 35 U.S.C. § 102 to support the present rejection. However, as discussed in detail above, the evidence and reasoning presented in the Office Action are incorrect, irrelevant, or both and do not establish that Kingsmore et al. discloses what the Office Action alleges.

Regarding the citations in the rejection to Kingsmore et al. column 42, lines 40-45; column 13, lines 59-66; and column 15, lines 5-20; and to Lizardi et al. column 11, lines 66-67; column 12, lines 1-10; column 14, lines 1-17; column 38, lines 44-55; and column 13, lines 14-19; applicants note that none of these passages are relevant to the intended claim limitations. For

example, column 42, lines 40-45 of Kingsmore et al. refers to analyte capture agents and bringing such analyte capture agents into contact with analyte samples. As defined in Kingsmore et al., analyte capture agents are "any compound that can interact with an analyte and allow the analyte to be immobilized or separated from other compounds and analytes." Column 13, lines 31-33. Thus, analyte capture agents are used in Kingsmore et al. to capture analytes (an example of this are the anti-IgE antibodies attached to the microarray in Example 7 of Kingsmore et al.; see microarray in Appendix A). This has nothing to do with amplification target circles, their association with a reporter binding molecule via a circle capture probe or their decoupling from a reporter binding molecule. Accordingly, the Office Action presents no credible evidence that Kingsmore et al. or Lizardi et al. disclose or suggest the claimed decoupling step.

For all of the above reasons, Kingsmore et al. and Lizardi et al., either alone of in combination, fail to make obvious claims 2-11.

Double Patenting Rejection

Claims 1, 12-113 and 118-136 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-72 of U.S. Patent No. 6,531,283 to Kingsmore et al. Applicants respectfully traverse this rejection.

The present rejection is based on misinterpretations of Kingsmore et al. and of the claimed method. Kingsmore et al. does not disclose or suggest what is alleged in the Office Action, and Kingsmore et al. does not disclose or suggest what is presently claimed. As a result, Kingsmore et al. fails to disclose every feature of the present claims. This error renders the rejection legally flawed with the result that the Office Action fails to establish a prima facie case

of obviousness-type double patenting. In making an obviousness-type double patenting rejection, the Patent Office is burdened with establishing that the cited patent teaches or suggests each and every limitation of the claims. The present rejection does not meet this burden.

Claims 1-72 of U.S. Patent No. 6,531,283 (the '283 patent) encompass methods of analyte detection that involve, *inter alia*, bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule binds to the analyte. An amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. None of the claims of the '283 patent recite that the amplification target circle is decoupled from the reporter binding primers. In fact, the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with the reporter binding primer during replication.

Applicants claim a method of detecting analytes that involves, *inter alia*, association of reporter binding molecules (which each comprise a specific binding molecule and an amplification target circle) with analytes. The amplification target circles are replicated to produce tandem sequence DNA. Significantly, however, the amplification target circles are decoupled from the reporter binding molecules prior to replication (see step (b) of claim 1; step (c) of claims 107, 108, and 110; lines 8-9 of claims 124 and 133; lines 12-13 of claim 134; lines 10-11 of claim 135; and lines 13-14 of claim 136). As described in the present application:

> decoupling refers to physical disunion of one molecule or component from another (as for example, decoupling of an amplification target circle from a reporter binding molecule). It is specifically contemplated that decoupling refers to the physical disunion both of molecules or components that are covalent couple [sic] to each other and molecules or components that are non-covalently associated with each other. In the former case, decoupling will generally involve cleavage of one of more covalent bonds. In the latter case, decoupling will generally involve dissociation.

Page 16, lines 19-26 of the application.

Applicants submit that Kingsmore et al. does not disclose or suggest any step of decoupling of an amplification target circle as required by the claims. No step in Kingsmore et al. corresponds to decoupling of an amplification target circle within the meaning of the term "decoupling" in the present application (see page 16, lines 19-26). Contrary to assertions in the rejection, the separations in Kingsmore et al. are not alternatives for the claimed decoupling. An unsupported (and erroneous) statement in the Office Action to the contrary does not make it so. At least because Kingsmore et al. fails to disclose or suggest decoupling of the amplification target circle from the reporter binding primers, Kingsmore et al. fails to disclose or suggest every feature of the claimed method. Accordingly, Kingsmore et al. fails to establish that claims 1, 12-113 and 118-136 are obvious variations of claims 1-72 of Kingsmore et al.

The Office Action asserts that the decoupling step is an obvious variation to the step of separating analyte capture agents from the analyte samples disclosed in the patented claims. Nowhere does the Office Action support the case that decoupling of an amplification target circle from a reporter binding primer is an obvious variation of the process of separating an analyte capture agent from an analyte sample. In the '283 patent, analyte capture agents "allow the analyte to be immobilized or separated from other compounds and analytes." On the other hand,

decoupling the amplification target from the reporter binding as presently claimed is used to free the amplification target circle for subsequent amplification. In fact, present claim 1 recites both the separation of "the specific binding molecules that interact with the analytes from the specific binding molecules that do not interact with the analytes" and the "decoupling the amplification target circles from the reporter binding molecule." Thus, these operations are not alternatives of the same process; rather, they are different, distinct processes. They are neither physically nor conceptually similar or analogous. Whether Kingsmore et al. discloses multiple separations does not cure the fact that the separations of Kingsmore et al. do not constitute a decoupling of the amplification target circle from a reporter binding molecule as presently claimed.

Further, the method of the '283 patent requires that the amplification target circle remain associated with the reporter binding primer since the reporter binding primer includes the rolling circle replication primer the method uses to replicate the amplification target circle. Thus, decoupling of the amplification target circle is inconsistent with the method claimed in Kingsmore et al. For all of these reasons, the presently claimed decoupling of amplification target circles from reporter binding molecules is not an obvious variation of any step or operation in the claims of the '283 patent. For at least these reasons, present claims 1, 12-113 and 118-136 are not obvious variations of claims 1-72 of the '283 patent. Accordingly, the present rejection cannot be sustained.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

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Respectfully submitted,

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